International Journal of Infectious Diseases 14 (2010) e458–e459

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

IFI = invasive fungal infections. What is that? A misnomer, because a non-invasive fungal infection does not exist!

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ARTICLE INFO

Article history:
Received 4 June 2009
Accepted 10 August 2009

Keywords:
Colonization
Invasion
Dermatophytes
Yeasts
Moulds

SUMMARY

In principle, one has to differentiate between a mere colonization and an invasive fungal infection (IFI) with quite different clinical manifestations and consequences. If the term invasive were used in its proper sense (*expressis verbis*), all fungal infections could be called invasive, even a fungal keratitis or an infection of the hairs by dermatophytes. In general, however, the term IFI is used only to characterize systemic, generalized, deep-seated, visceral and severe, life-threatening fungal infections, in contrast to superficial, local, benign, self-limiting fungal diseases. The term IFI as used generally is thus misleading, confusing, and not at all helpful to correctly differentiate mild, moderate, and severe fungal infections.

IFI = invasive fungal infections

Clinicians often use the term invasive fungal infection (IFI) to describe a severe, systemic infection with yeasts or moulds.[1] Recently, a revised definition has been given by an expert group.[2] But does this term really help to distinguish invasive fungal infections from other fungal infections?

Dermatophytes are able to penetrate the keratinized layers of the skin. This first step triggers an inflammatory response characterized by an attraction of neutrophilic granulocytes and macrophages. Furthermore, this local infection called tinea, leads to a systemic T-lymphocyte response as well as to a production of antibodies, which can be detected in the blood. In some instances such immune phenomena may be responsible for pathologic tissue reactions even at distant, non-infected sites.[3] Some dermatophytes, for example *Trichophyton violaceum*, are characterized by an invasion of hair shafts and an endothrix parasitism within the hairs of the affected patient.[4] Because serum components will inhibit the growth of dermatophytes and because keratin, the essential nutrient, is not available in deeper tissues, infections will remain superficial.[3,5] But any way, these local infections will cause a systemic immune response.

Following local damage, *Fusarium spp* are able to penetrate into the cornea, to propagate into the direct vicinity, and to induce more or less extensive keratitis.[6] In general, this infection will remain restricted to the portal of entry.

Candida albicans frequently colonizes the vagina of women without inducing any symptoms. This saprophytic state can switch to an invasive situation under certain predisposing conditions. In pregnant women and women taking oral contraceptives these fungi, which possess several virulence factors, invade the epithelial layer and trigger a local inflammatory reaction leading to vaginal mycoses.[7,8] Other dermal and mucosal sites may first be colonized and then invaded by *C. albicans*, too, inducing thrush. In immunocompromised patients these opportunistic fungi tend to infiltrate deeper tissues and may even disseminate to distant organs, inducing visceral candidiasis.[3] Both local and disseminated infections are due to invasion!

Cryptococcus neoformans is widespread in nature. When these yeasts are inhaled by humans or animals they are able to survive within the alveolar macrophages of the host and multiply locally in the lung, inducing a focal inflammatory reaction. Although in most instances these transitional cryptococcoma are not recognized and are overlooked, they may function as the secondary source for a dissemination to other organs such as the brain, prostate, etc.[9] Quite similarly, spores of dimorphic fungi, such as *Coccidioides immitis*, are distributed via air and are inhaled. Initially, they invade the lung and induce a localized, nodular inflammatory response; in most instances a self-limiting pulmonary infection occurs; occasionally the lung infection persists and the fungi infiltrate larger zones. In particular when cell-mediated immunity is impaired, the fungi spread from the primary manifestation site

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doi:10.1016/j.ijid.2009.08.006

to other, distant organs where they may also produce granulomatous reactions. The consequences of infection with *C. immitis* may vary, and the local area of tissue damage in an organ may be small, i.e. nodular, or large, i.e., diffuse.[10] Obviously, all stages of this fungal infection are invasive!

Zygomycetes commonly residing in the environment are taken up by inhalation into the nasal sinuses. Whereas in most instances this confrontation does not induce harm, occasionally they invade the mucosal layer. These initial stages of an invasive fungal infection are often overlooked, since the symptoms are not yet overt. However, in susceptible individuals presenting diabetes or hematologic malignancies, this first step of a local infection may be followed by dissemination into various internal organs and even into bone structures;[11] then the prognosis is rather poor.

Spores of *Aspergillus fumigatus* are almost ubiquitous in nature; they frequently reach the respiratory tract. If they are deeply inhaled, they may be phagocytosed by the alveolar macrophages. Whereas in general the spores are eliminated rapidly, in an immunocompromised host, for example one treated with corticosteroids, the fungal cells survive and hyphae may penetrate into the lung tissue. In many such cases the aspergillosis of the lung is further complicated by hematogenous dissemination to virtually all distant organs.[12] Some forms of invasive aspergillosis of the lung are, however, preceded by a superficial, localized stage. For example the aspergilli may settle in the nasal sinuses and sphenoid sinuses[13,14] and occasionally they may persist and even grow locally, producing a so-called fungus ball, i.e., a non-invasive, extramucosal mycetoma. This massive assembly of fungal hyphae is not a common source of invasion of the surrounding tissues; occasionally, however, this internal colonization shifts into an infection due to invasion of the mucosal layers and the adjacent bone structures.[15] Such fungus balls may also develop in preformed cavities of the lung. The non-invasive fungus ball may reside within the host for decades in these deep-seated locations, before the fungal hyphae eventually penetrate into the lung tissue and induce pulmonary aspergillosis.[16] An uncommon manifestation of invasive pulmonary aspergillosis is tracheobronchitis;[17] in such cases the infection is restricted to the mucosa leading to the local obstruction of the airways. Large and extended scald or burn wounds of the skin are often contaminated aerially with spores of *A. fumigatus*. Fungal colonies spread over these surfaces; this quite superficial infection is often accompanied by an invasion of hyphae into the upper layer of the wounds, leading to a limited inflammatory reaction. Obviously, *A. fumigatus* can either colonize or invade a host more or less intensively.

In conclusion, one has to differentiate between a mere saprophytic colonization and an invasive fungal infection with quite different clinical manifestations and consequences. If the term invasive were used in its proper sense (*expressis verbis*), all fungal infections could be called invasive, not only those with radiological signs or elevated galactomannan levels in the serum![2] In general, however, the term IFI is used exclusively to characterize a systemic, generalized, deep-seated, visceral and severe, life-threatening fungal infection,[1,2] rather than a superficial, local, benign, self-limiting fungal disease. Apart from the 'so-called IFIs', such as a lung aspergillosis, it should be kept in mind that the so-called non-IFI fungal infections, such as skin infections by dermatophytes, are also invasive.

Thus this term, as used generally, is misleading, confusing, and not at all helpful, since invasiveness can tell the difference between colonization and infection, but obviously is inadequate to differentiate clearly between mild, moderate and severe fungal disease. For these various entities with quite different prognoses and which each require quite different therapeutic approaches, another, more convenient terminology is warranted; for example the term ominous or life-threatening fungal infection would point out the urgent need for diagnostic and therapeutic measurements.

The term invasive fungal disease (IFD), proposed recently,[2] is not a good alternative to describe only the advanced stages of fungal infections, because an initial, local stage of disseminated fungal infection, a superficial mucosal infection, a fungal keratitis, or even an infection of the hairs by dermatophytes, which are all a consequence of invasion by fungi, represent definite signs of sickness and also merit this label.

Conflict of interest: The author has received a fee for speaking from Schering-Plough, MSD, Pfizer, Gilead and Astellas; a fee for organizing education from Pfizer; a fee for serving on advisory boards from Schering-Plough, MSD, Gilead and Astellas. This paper was written without any sponsorship.

References

1. Badiee P, Kordbachev P, Alborzi A, Malekhoseini S, Ramzi M, Mirhendi H, et al. Study on invasive fungal infections in immunocompromised patients to present a suitable early diagnostic procedure. *Int J Infect Dis* 2009;**13**:97–102.
2. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813–21.
3. Brasch J. Current knowledge of host response in human tinea. *Mycoses* 2009;**52**:304–12.
4. Morar N, Dlova NC, Gupta AK, Aboobaker J. Tinea capitis in Kwa-Zulu Natal, South Africa. *Pediatr Dermatol* 2004;**21**:444–7.
5. King RD, Khan HA, Foye JC, Greenberg JH, Jones HE. Transferrin, iron and dermatophytes. Serum dermatophyte inhibitory component definitely identified as unsaturated transferrin. *J Lab Clin Med* 1975;**86**:204–12.
6. Sirikul T, Prabriputaloong T, Smathivat A, Chuck RS, Vongthongsri A. Predisposing factors and etiologic diagnosis of ulcerative keratitis. *Cornea* 2008;**27**:283–7.
7. Lian CH, Liu WD. Differential expression of *Candida albicans* secreted aspartyl proteinase in human vulvovaginal candidiasis. *Mycoses* 2007;**50**:383–90.
8. Sobel JD. Vulvovaginal candidosis. *Lancet* 2007;**369**:1961–71.
9. Casadevall A, Perfect JR. Cryptococcus neoformans. Washington: ASM Press; 1998.
10. Bronnimann DA, Galgiani JN. Coccidioidomycosis. *Eur J Clin Microbiol Infect Dis* 1989;**8**:466–73.
11. Islam MN, Cohen DM, Celestina LJ, Ojha J, Claudio R, Bhattacharyya IB. Rhinocerebral zygomycosis: an increasingly frequent challenge. Update and favorable outcomes in two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**104**:e28–34.
12. Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)* 2000;**79**:250–60.
13. Costa F, Polini F, Zerman N, Robiony M, Toro C, Politi M. Surgical treatment of Aspergillus mycetomas of the maxillary sinus: review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**103**:e23–9.
14. Bowman J, Panizza B, Ghandi M. Sphenoid sinus fungal balls. *Ann Otol Rhinol Laryngol* 2007;**116**:514–9.
15. Han DH, An SY, Kim SW, Kim DY, Rhee CS, Lee CH, et al. Primary and secondary fungal infections of the paranasal sinuses: clinical features and treatment outcomes. *Acta Otolaryngol Suppl* 2007;**558**:78–82.
16. Terzi A, Furia S, Biondani G, Calabrò F. Sequential left pneumonectomy and right upper lobectomy for hemoptysis in post-tuberculosis destroyed lung and aspergilloma. *Minerva Chir* 2008;**63**:175–9.
17. Mohan A, Guleria R, Mukhopadhyaya S, Das C, Nayak A, Sharma SK. Invasive tracheobronchial aspergillosis in an immunocompetent person. *Am J Med Sci* 2005;**329**:107–9.